PLASMA CELL NEOPLASIA

Michael Miller, MD & Ajaz Shawl, MD
Plasma Cell Neoplasia

- Board Questions
- Case Presentation
- Introduction
- Epidemiology
- Presentation
- Diagnosis
- Laboratory Tests
- Imaging
- Differentials
- Treatment
- Prognosis
BOARD QUESTIONS
61. A 62-year-old female presents with numbness and tingling in her feet. She first noticed tingling in the toes of her right foot several months ago; it is now present in both feet and is causing numbness. She has not experienced any weakness, or any changes in vision, speech, or memory. Her medical history includes hypertension controlled by lisinopril (Prinivil, Zestril), 20 mg daily, and she also takes aspirin, 81 mg daily. She drinks a glass of wine nightly and does not smoke. She does not have a family history of neurologic disorders.

On examination she has symmetric decreased sensation to light touch and vibration in her feet. Reflexes and strength are intact bilaterally. Laboratory findings include a normal CBC and normal TSH and vitamin B₁₂ levels. Her erythrocyte sedimentation rate is 32 mm/hr (N 0–20). A comprehensive metabolic panel is normal except for a total protein level of 8.5 g/dL (N 6.0–8.3).

Which one of the following tests would be most useful for making a diagnosis?

A) An angiotensin converting enzyme level
B) Serum protein electrophoresis
C) A chest radiograph
D) A lumbar puncture with cerebrospinal fluid analysis
E) MRI of the lumbar spine
Item 61

ANSWER:  B

This patient has a peripheral neuropathy. A review of the patient’s history and specific laboratory testing was performed to evaluate for the most common treatable causes of peripheral neuropathy, which include diabetes mellitus, hypothyroidism, and nutritional deficiencies. Additional causes of peripheral neuropathy include chronic liver disease and renal disease. It is important to consider medications as a possible cause, including amiodarone, digoxin, nitrofurantoin, and statins. Excessive alcohol use is another important consideration. In this patient, the mildly elevated total protein and erythrocyte sedimentation rate, which suggest a monoclonal gammopathy such as MGUS (monoclonal gammopathy of unknown significance) or multiple myeloma, should direct her workup. Serum protein electrophoresis is indicated to assess for this.

Other less common causes of peripheral neuropathy include carcinoma causing a paraneoplastic syndrome, lymphoma, sarcoidosis, AIDS, and genetic disorders such as Charcot-Marie-Tooth disease. Approximately 25% of patients with peripheral neuropathy have no clearly defined cause after a thorough evaluation and are diagnosed with idiopathic polyneuropathy.

MRI of the lumbar spine can identify central lesions causing spinal cord or nerve root compression but is not indicated in the evaluation of peripheral neuropathy. Serum angiotensin converting enzyme levels and a chest radiograph can assist in the diagnosis of sarcoidosis, which can cause peripheral neuropathy but is less likely in this patient. Cerebrospinal fluid analysis is important in assessing for chronic inflammatory demyelinating polyradiculoneuropathy, a more rare cause of peripheral neuropathy.
148. A 66-year-old male is diagnosed with monoclonal gammopathy of undetermined significance. This patient will require regular follow-up visits because of the risk his condition will progress to

A) aplastic anemia
B) multiple myeloma
C) chronic lymphocytic leukemia
D) acute myelogenous leukemia
E) idiopathic thrombocytopenic purpura
Item 148

ANSWER: B

Monoclonal gammopathy of undetermined significance (MGUS) is present in approximately 2%–3% of the white population older than 50. It is associated with a risk of progression to multiple myeloma at a rate of 1% per year. Most patients diagnosed with MGUS should be reevaluated in 6 months with a medical history, physical examination, CBC, calcium and creatinine levels, and serum electrophoresis, and then annually thereafter.

12. One of your patients has been diagnosed with monoclonal gammopathy of undetermined significance (MGUS). Which one of the following is used to determine whether his condition has progressed to multiple myeloma?

A) The length of time since the diagnosis of MGUS was made
B) The level of M protein
C) The percentage of plasma cells in bone marrow
D) Evidence of end-organ damage
Item 12

ANSWER: D

The diagnosis of multiple myeloma is based on evidence of myeloma-related end-organ impairment in the presence of M protein, monoclonal plasma cells, or both. This evidence may include hypercalcemia, renal failure, anemia, or skeletal lesions. Monoclonal gammopathy of undetermined significance does not progress steadily to multiple myeloma. There is a stable 1% annual risk of progression.

207. A previously healthy 60-year-old male is diagnosed with multiple myeloma after a workup for an incidental finding on routine laboratory work. He has no identified organ or tissue damage and is asymptomatic.

Which one of the following would be appropriate treatment of this patient’s condition?

A) No treatment
B) Chemotherapy
C) Autologous stem cell transplantation
D) Radiation
Item 207

ANSWER: A

This patient has smoldering (asymptomatic) multiple myeloma. He does not have any organ or tissue damage related to this disease and has no symptoms. Early treatment of these patients does not improve mortality (SOR A) and may increase the likelihood of developing acute leukemia. The standard treatment for symptomatic patients under age 65 is autologous stem cell transplantation. Patients over 65 who are healthy enough to undergo transplantation would also be appropriate candidates. Patients who are not candidates for autologous stem cell transplantation generally receive melphalan and prednisolone with or without thalidomide. Radiotherapy can be used to relieve metastatic bone pain or spinal cord compression.

PLASMA CELL NEOPLASIA MASQUERADING AS BONY METASTASIS

Case Presentation
Patient History

- 53 year old male with a past medical history significant for **chronic back pain** of four months duration, presents with complaints of **worsening mid/low back pain over the past four weeks** associated with “lightheadedness,” chest pain and shortness of breath. He had no history of trauma and no inciting event.

- Seen in the ED three months prior complaining of back pain; had a negative x-ray of the thoracic spine, given Norco and discharged with a lidocaine patch.

- Had been seen for an establish care office visit two months prior to admission with complaints of back pain; prescribed PT, NSAIDs and flexeril. Had also ordered labwork including CBC, CMP which patient never had done.

- He was also complaining of **bowel incontinence and lower extremity weakness** but had no urinary incontinence. Symptoms had been ongoing for weeks.
Physical Exam

- Vitals: Afebrile - 97.3, HR 101, BP -121/81

- Disheveled, in no apparent distress. Ambulating with a cane. Tachycardic.

- **Tenderness to palpation** over the lumbar spinous processes worsened by passive and active range of motion. No CVA tenderness.

- Orthopedic Consult Physical Exam:
  - Lower extremities with intact motor and sensate. 5/5 strength noted to hip, knee and ankle flexion and extension. 2+ radial and dorsalis pedis pulses.
## Initial Labwork in the ED

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<th>Notes</th>
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<td>4.1 - 11.0 x 10^3/ul</td>
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<tr>
<td>RBC</td>
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### Electrolytes

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<td>CO2</td>
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<td>Anion Gap</td>
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<td>Urea nitrogen</td>
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<td>Glucose</td>
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### Additional Parameters

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<td>GFR MDRD Af Amer</td>
<td>21</td>
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<td>Glom Filt Rate, Est</td>
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### Lab Values

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<td>Globulin</td>
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<td>RATIO</td>
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<td>Bilirubin, Total</td>
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<td>Bilirubin, Direct</td>
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<td>0.0 - 0.3 mg/dL</td>
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<tr>
<td>Bilirubin, Indirect</td>
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<td>0.0 - 0.7 mg/dL</td>
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<tr>
<td>Alkaline</td>
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<tr>
<td>Phosphatase</td>
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<tr>
<td>AST</td>
<td>15</td>
<td>11 - 39 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>22</td>
<td>12 - 78 U/L</td>
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**Resulting Agency:** LAB ALLIANCE
Imaging

X-Ray of Lumbar Spine – Multiple compression fractures and severe osteopenia. No lytic or blastic lesion is demonstrated.

Chest X-Ray – Cannot exclude left lower lobe pulmonary nodule.

CT Chest – Innumerable low density lesions seen throughout the thoracic, lumbar spine and ribs consistent with extensive metastatic disease.
Diagnosis and Evaluation

- In the setting of acute kidney injury, hypercalcemia, and thoracic lumbar compression fractures, there was initial concern for multiple myeloma, or possibly bony metastasis with an unknown primary.

- The initial work up included SPEP, UPEP, PTH, ESR, CRP, Urinalysis including electrolytes and protein/creatinine ratio, PSA, iron panel, troponin, BNP.

- CT Abdomen/Pelvis was ordered to evaluate for primary site of cancer.

- MRI spine was ordered to rule out spinal cord compression but unable to be performed due to bullet fragments in the patient’s gluteus.

- Hematology/Oncology, Nephrology, Orthopedics were consulted.

- A Bone Biopsy was performed to evaluate lesions.
Workup Results

- **PTH** - 4.2 pg/mL  **NORMAL**
- **CRP** - 1.8, ESR – 58 **HIGH**
- **Troponin** <0.06 **NORMAL**
- **Ferritin** - 1,388 ng/mL **HIGH**
- **Beta-2 Microglobulin** - 8.0 mg/L  **HIGH**
- **SPEP** – No monoclonal identified. No paraprotein detected by serum protein electrophoresis.
- **IgG, IgA levels normal.** PSA normal.
- **UPEP** – Ordered but not collected.
- **CT Abdomen** –
  - Moderate rectal wall thickening with some surrounding inflammatory change. Might consider colonoscopy to exclude rectal malignancy.
  - Patchy lucency throughout the bones compatible with diffuse osseous metastatic disease
CT guided right iliac bone biopsy
KAPPA-Restricted Plasma Cell Neoplasm. Sections of the biopsy show sheets of CD138 positive plasma cells infiltrating the bone marrow, accounting for 60% of cellularity. ISH study shows that the plasma cells are Kappa restricted. Lambda stains rare cells. Overall findings are consistent with kappa-restricted plasma cell neoplasm.
MULTIPLE MYELOMA
Introduction

- **Plasma cell myeloma** is a bone marrow based plasma cell neoplasm *usually* associated with an M-protein in serum or urine. The bone marrow is the site of origin of nearly all myelomas. The diagnosis of myeloma is made by a combination of clinical, morphological, immunologic and radiographic information.

- **Multiple Myeloma** evolves from a pre-malignant condition clinically recognized as *monoclonal gammopathy of undetermined significance* (MGUS).

- It accounts for 1% of all cancers worldwide and 10-15% of all hematological neoplasms.

- Modern treatment plans have *increased the 5 year survival* rate for myeloma patients up to 75 years of age to over 50%.

- Until 2000, the mainstay of therapy was alkylators and corticosteroids; subsequently **thalidomide, bortezomib and lenalidomide emerged as effective agents** and improved clinical outcome.
Hematopoiesis
Epidemiology

- **Incidence**
  - Approximately 20,000 cases diagnosed in USA in 2008
  - 1% of all cancers and 2% of all cancer deaths
  - 10-15% of hematopoietic malignancies

- **Genetic Predisposition**
  - 40% of plasma cell myeloma patients have a first degree relative with cancer; 10% of these are hematologic neoplasms

- **Age**
  - Peak incidence is in the 8th decade of life
    - Rarely observed in people less than 35 years of age
    - Median age at diagnosis is 66 years.

- **Sex**
  - Slight male predominance
  - M:F ratio is 3:2

- **Ethnicity**
  - High Incidence in African Americans: 9.5/100,000
  - Caucasian American incidence is 4.1/100,000

- **Environmental Exposure**
  - Linked to chemical, toxin or radiation exposure
    - Herbicides, insecticides, asbestosis, rubber, plastic, wood or petroleum products, radiation from atom bomb (Japan), nuclear plants
Presentation

- Unique triad: Bone marrow plasmacytosis, osteolytic bone lesions, monoclonal gammopathy
  - Clinical and laboratory findings reflect or are secondary to these abnormalities
    - Bone pain and pathological fractures
    - Fatigue
    - Weight loss
    - Anemia of chronic disease
    - Renal failure
    - Recurrent bacterial infections from hypogammopathy and immunodeficiency
    - Symptoms from hypercalcemia
      - Nausea, fatigue, thirst.
    - Symptoms of hyperviscosity
      - Headaches, bruising, ischemic neurologic symptoms
Laboratory Tests

- **Serum protein electrophoresis (SPEP)**
  - Identifies and quantifies monoclonal protein (M-component)
  - Immunofixation electrophoresis to determine immunoglobulin type
  - IgG > 50%, IgA 20-25%, light chain 20%
  - Decrease in uninvolved immunoglobulins (90% of cases)

- **Urine protein electrophoresis (UPEP) or serum free light chain (FLC) assay**
  - FLC is best for screening
  - If abnormal, perform UPEP; requires 24-hour urine collection
  - Bence-Jones protein in urine

- **Peripheral blood and bone marrow examination**
  - Perform ancillary tests on bone marrow
  - Red blood cells show Rouleaux formation

- **Chemical panel**
  - Increased beta 2 macroglobulin (75% at diagnosis)
    - Surrogate marker for tumor burden
  - Subset of patients have increased uric acid, creatinine, calcium, decreased albumin
  - Low/normal alkaline phosphatase
Rouleaux Formation
Lytic Bone lesions

- Whole-body low-dose CT is recommended for diagnosis of lytic disease
- Conventional radiography can be used if WBLD-CT is not available
- MRI provides greater details and is recommended whenever spinal cord compression is suspected.
Diagnostic Criteria for Plasma Cell Myeloma

Clonal BM plasma cells >10% or biopsy-proven plasmacytoma and anyone or more of the following myeloma defining events

End-organ damage attributable to the plasma cell disorder

- Hypercalcemia:
  - serum calcium >11 mg/dL

- Renal insufficiency:
  - Creatinine clearance of <40mL per min or serum creatinine >2 mg/dL

- Anemia:
  - Hemoglobin <10g/dL

- Bone Lesions
  - One or more osteolytic lesions on skeletal radiography, CT, or PET-CT

One or more of the following biomarkers of malignancy

- Clonal bone marrow plasma cell percentage > 60%

- Involved: uninvolved serum free light chain ratio > 100

- >1 focal lesions on MRI studies
Differential Diagnosis

- **Monoclonal Gammopathy of Undetermined Significance (MGUS)**
  - Small clonal PC population (<10%), small paraprotein
    - No signs of disease-related, end-organ damage or bone lesions
  - Serum M-protein < 3 g/dL
  - Bone marrow plasma cells < 10%
  - Absence of anemia, renal failure, hypercalcemia, lytic bone lesions
  - Approximately 1-2% of these patients progress to a more malignant condition

- **Asymptomatic Multiple Myeloma**
  - Smoldering Multiple Myeloma
    - Serum M-protein > 3 g/dL and/or bone marrow plasma cells > 10%
    - No anemia, renal failure, hypercalcemia, lytic bone lesions
    - Stable serum/urine M-protein

- **Bone Metastasis**
  - Breast, prostatic, colon cancer
Classification – Durie and Salmon Staging System

- **Stage I (low cell mass)** 600 billion myeloma cells
  - Hemoglobin > 10 g/dL
  - Serum calcium normal or <10.5 mg/dL
  - Bone X-ray, normal bone structure
  - Low M-component production rates (IgG <5.0g/dL, IgA <3.0g/dL)
  - Urine light chain M component on electrophoresis < 4g/24h

- **Stage II (intermediate cell mass)** 600 to 1,200 billion myeloma cells
  - Fitting neither stage I nor stage III

- **Stage III (high cell mass)** >1,200 billion myeloma cells
  - One or more of the following
    - Hemoglobin <8.5
    - Serum calcium >12 mg/dL
    - High M-component production rates (IgG >7.0g/dL, IgA >5.0g/dL)
    - Urine light chain M-component >12g/24h
International staging system

- B2M = serum beta 2 macroglobulin in mg/L
- Alb = Serum albumin in g/dL

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<th>Class</th>
<th>Criteria</th>
<th>Survival (months)</th>
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<tbody>
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<td>Stage I</td>
<td>B2M &lt;3.5 Alb &gt;3.5</td>
<td>62</td>
</tr>
<tr>
<td>Stage II</td>
<td>B2M &lt;3.5 Alb &lt;3.5</td>
<td>44</td>
</tr>
<tr>
<td>Stage III</td>
<td>B2M &gt;5.5</td>
<td>29</td>
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</table>
Treatment

- **Novel Therapeutics**
  - Immunomodulatory drugs and Proteasome Inhibitors
  - Utilized in specific subset of patients (many in clinical trials)
    - Elderly patients, patients with relapsed/refractory disease, severe renal failure
  - Melphalan/prednisone/thalidomide (MPT)
  - Levaldome/low dose dexamethasone (Revlodex)
  - Bortezomib/melphalan/prednisone (VMP)

- **Stem Cell Transplantation**
  - Patients eligible typically have no significant comorbidities, younger than 75 years of age.
  - **Autologous** vs. allogenic
  - Prolongs survival

- **Conventional Chemotherapy**
  - Melphalan
  - Doxorubicin
  - Cyclophosphamide

- **Steroid therapy**
  - Dexamethasone
  - Prednisone
Treatment

- **Supportive**
  - Radiotherapy
  - Surgery
    - Laminectomy, spinal fusion in cases of instability
  - Bisphosphonates
  - Transfusions

- **Complications**
  - Uremia – hydration, diuretics, steroids, hemodialysis
  - Hypercalcemia – rehydration, steroids, bisphosphonates, diuretics
  - Paraplegia – decompressive laminectomy, radiotherapy, chemotherapy
  - Bone lesions – if painful and localized, chemo or local radiotherapy, bisphosphonates
The hallmark of multiple myeloma is the finding of a paraprotein on serum or urine protein electrophoresis or immunofixation electrophoresis.

Approximately 15% of patients will have no demonstrable paraprotein in the serum because their myeloma cells produce only light chains and not intact immunoglobulin. The light chains pass rapidly through the glomerulus into the urine.

This patient's clinical picture was clouded by the
- 1) Negative SPEP
- 2) Lack of osteolytic lesions
- 3) Rectal wall thickening on the CT scan which was the presumed primary cancer.
Conclusion and Teaching Points

- Bone marrow biopsy revealed kappa restricted plasma cell neoplasm, diagnosed as **Light Chain Multiple Myeloma** due to combination of clinical, immunologic and radiographic findings.

- Ultimately, the patient was transferred to another hospital for **chemotherapy and radiation therapy to spine** in stable condition.

- **LCMM** tends to have a poor prognosis and there are no established guidelines for management.
References


